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MOLECULAR AND GENETIC RISK FACTORS FOR THE DEVELOPMENT OF THROMBOTIC AND HEMORRHAGIC COMPLICATIONS IN ESENTIAL THROMBOCYTHEMIA
(Literature review).

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Report. Essential thrombocythemia (ET) is a pathology of clonal hematopoietic stem cells that leads to increased platelet production. Pathogenetically, ET is a bone marrow disease in which megakaryocyte proliferation leads to persistent hyperthrombocytosis with the risk of vascular thrombosis and thromboembolism. The etiology of the disease has not yet been established. The leading hypothesis is the polyethological nature of the disease occurrence, where the predisposition to the disease is realized under the influence of external factors that damage the genome of a normal cell and lead to its malignant transformation
Molecular genetic analysis *of JAK2*V617F, *JAK2* exon12, *MPL*W515K/L, and *CALR mutations* plays an exceptional role in the diagnosis of classic Ph-negative MPN. However, genes that control signal transmission within the cell, chromatin remodeling, DNA methylation, oncogenes, and tumor suppressors are involved in the development of these diseases. Current knowledge suggests that *the JAK2*V617F mutation may not be the first event in the complex pathogenesis of myeloproliferative diseases (MPD). This review describes the current understanding of molecular genetic disorders that are risk factors and affect the development of thrombotic and hemorrhagic complications in ET.
Key words: chronic myeloproliferative diseases, essential plateletмformation, primary myelofibrosis, JAK2 gene , MPL gene, CALR gene, triple-negative status.

Essential thrombocythemia (ET) is a chronic tumor myeloproliferative disease of a clonal nature, characterized by megakaryocyte proliferation and persistent thrombocytosis [3, 2, 20]. ET is a rare (orphan) disease. There are no population-based epidemiological data on morbidity and prevalenceëin Uzbekistan. The morbidity rate, according to foreign registries [4, 6, 14], is approximately 1.5-2.53 per 100,000 population. Classical ideas about ET as a disease mainly of elderly people with a maximum incidence of 50-60 years are currently being revised. The discovery of the involvement of molecular genetic breakdowns (mutations in *JAK2, MPL*, etc.) in the pathogenesis of the disease and the introduction of methods for their determination into clinical practice made it possible to identify a significant proportion of young patients [8, 29]. The ratio of women to men is approximately equal. However, there are slightly more women than men among young patients [35].
The main reason leading to disability and reduced life expectancy in ET is the development of thrombosis and thromboembolism. The cumulative risk of clinically significant thrombosis is 5% for the duration of the disease of 5 years and 14% for the duration of ET of 10 years [2, 3]. With a prolonged course of the disease, secondary post-platelet myelofibrosis may occur in 3-10% of patients during the first 10 years of the disease and in 6-30% of patients with a disease duration of more than 10 years [31, 23, 32]. Progression of the disease to the blast transformation phase is observed in 1-2. 5% during the first 10 years of the disease and in 5-8% of patients with a disease duration of more than 10 years [23, 32, 28].
The etiology of the disease has not yet been established. The leading hypothesis is the polyethological nature of the disease occurrence, where the predisposition to the disease is realized under the influence of external factors that damage the genome of a normal cell and lead

toë its malignant transformation [1, 25, 52, 13]. Hereditary predisposition to the disease may be due to the carrier of the 46/1 haplotype of the JAK2 gene [10].
The clinical course of the disease is closely related to its pathogenesis. At the initial stage of development, there is a gradual increase in the tumor mass. During the first years of the disease, the main manifestations of ET are an increased risk of developing thrombosis and thromboembolism against the background of existing cardiovascular pathology and atherosclerosis. Leukocytosis and thrombocytosis can lead to microcirculation disorders and the development of thrombosis. The occurrence of thrombosis in ET is always the result of the interaction of changes caused by the disease and multiple risk factors for thrombosis. Factors contributing to the development of thrombosis can be divided into two groups: [1, 19].
1. Factorsassociated with the disease: thrombocytosis, leukocytosis, interaction between leukocytes and platelets, biochemical and functional abnormalities in platelets, activationof theblood clotting process, the presence *of JAK2* V617F mutation and a high allelic load.
2. Individual factors of the patient: age, history of thrombosis, risk of cardiovascular complications, thrombophilia.
An increase in the concentration of procoagulant microparticles produced by both platelets and endothelial cells also contributes to the increased risk of thrombosis [49]. The cumulative risk of clinically significant thrombosis is 5% with a disease duration of 5 years and 14% with a ten-year history of ET [23].

Uncontrolled activation of the cellular signaling pathway JAK-STAT is a key element in the pathogenesis of ET. Currently, the central role of somatic point mutation of the gene encoding tyrosine *kinase JAK2* (*JAK2*V617F), in the activation of the JAK-STAT pathway has been reliably established. The discovery of the mutation in 2005 and the subsequent study of its role in the pathogenesis of ET radically changed the existing ideas about the origin and development of the disease, led to a radical revision of existing ideas about the pathogenesis of the disease, which made it possible to form a new diagnostic algorithm for ET and contributed to the inclusion of mutation in the diagnostic algorithm of ET. However, the presence *of JAK2*V617F only in 50-60% of patients revealed the need to search for other genetic rearrangements involved in the development of clonal myeloproliferative process *in JAK2*V617F-negative patients. [4].

Activation *of JAK2* kinase, mutation in the MPL thrombopoietin receptor gene*, and loss of function of the LNK gene of the SH2B3 protein, which inhibits JAK2 activity, may be one of the key pathogenesis factors and a probable molecular genetic mechanism of ET development* и потеря функции гена LNK белка SH2B3, ингибирующего активность *JAK2* [51].
Pathogenetically, ET is a clonal myeloproliferative process that develops as a result of malignant transformation in early hematopoietic progenitors with a violation of cellular signaling pathways that regulate cell growth, activation, differentiation, adhesion, and apoptosis [13]. A significant (25-55%) proportion of patients with ET is characterized by the detection of a point mutation in the januskinase gene of the erythropoietin receptor *JAK2V617F* [16, 25, 42]. Also, some patients may have mutations in the genes of the thrombopoietin receptor-*MPL* and *TET2* [39, 30],
The diversity of the phenotype of myeloproliferative neoplasms (MPN) is determined by genetic heterogeneity. Mutations primarily affect genes that control cytokine signaling pathways. The JAK-STAT pathway plays a crucial role in the proliferation and differentiation of hematopoietic cells. In patients with MPN, a somatic JAK2 mutation is detected with a high frequency*JAK2*, most often *JAK2*V617F. Since 2008. The main diagnostic criteria for IP, ET, and PMF included the presence *of the JAK2*V617F mutation. After the discovery *of JAK2*V617F, other mutations in the gene were also identified [*38*].

At the present stage, the role of somatic point mutation of the JAK2 tyrosine kinase gene (*JAK2*V617F) in the activation of the JAK-STAT pathway in Ph-negative MPN is indisputable. Mutation detection is central to the diagnosis of ET [47].

Activation of the JAK-STAT signaling pathway is an important pathogenetic event in classical Ph-negative MPN. In PMF and ET, half of the patients have acquired *the JAK2*V617F mutation. In addition, other components of the JAK-STAT signal transduction pathway are an important regulator of hematopoiesis [6].

Thus, *the JAK2*V617F mutation is a specific molecular genetic marker of the clonal myeloproliferative process in ET. With a comprehensive diagnostic approach, combined with other criteria, the detection *of JAK2*V617F makes it possible to reliably and reasonably establish the diagnosis of ET in 50-60% of patients.

However, in the remaining 40-50% of patients, the genetic basis of clonal myeloproliferation remained unknown. The persistence of a significant number *of JAK2*-negative patients, whose disease genesis remained poorly understood, revealed the need to search for new molecular genetic markers of clonality in this category [5].
Current knowledge suggests that *the JAK2*V617F mutation may not be the first event in the complex pathogenesis of ET. Additional studies are needed to clarify the role of other molecular events in the formation of the phenotype of each individual nosology in the Ph-negative MPN group. The new data are of indisputable importance for the synthesis of targeted drugs.

As a result of the search for other molecular genetic markers of clonality, two types of somatic mutations were identified that are also involved in the activation of the JAK-STAT pathway. In 2006, somatic mutations of the thrombopoietin receptor gene*, MPL, were described*, and in 2013, mutations of the gene encoding the protein calreticulin, *CALR*. The study of the effect *of MPL* and *CALR mutations* on the pathogenesis of ET is currently ongoing.

Another gene involved in the regulation of the JAK-STAT signaling pathway is the thrombopoietin receptor gene. Binding of thrombopoietin to this receptor regulates megakaryocyte maturation and platelet lacing by activating the JAK-STAT pathway [24]. Мутации *MPL mutations* (most commonly W515L) have been described in patients with PMF and ET.
The thrombopoietin receptor (*MPL*) gene belongs to the cytokine receptor superfamily, located on chromosome 1p34 and includes 12 exons. Thrombopoietin, after binding to the extracellular domain of the receptor, causes phosphorylation and activation of tyrosine kinase JAK2, phosphorylation and activation of MPL, and signal transmission via the STAT pathway. Studies have shown that the level of MPL receptor expression is important for the onset and progression of MPN [18,37].
Mutations *of the MPL gene* do not occur in patients with ET, but can be detected in patients with secondary acute myeloid leukemia (AML). They can occur both in isolation and together with *JAK2*V617F with a higher allelic load *of the MPL mutation*. The frequency of detection *of MPL*W515L and *MPL*W515K mutations in patients with PMF and ET is 1-15% [12, 7].
In the presence *of the MPL mutation*, the disease is characterized by high thrombocytosis, normal erythropoietin levels, low hemoglobin content, and low bone marrow cellularity. *The MPL mutation* compared to *JAK2*V617F is a more significant risk factor for thrombotic complications and the development of transfusion-dependent anemia [12, 48]. The association between

splenomegaly, abnormal karyotype, risk of transformation of the disease into post -platelet myelofibrosis (MF) or AML and the presence of mutations *in the MPL gene has not been proven*. Nevertheless, clinical cases have been described where a high risk of thrombosis, massive splenomegaly, and bone marrow fibrosis was observed in familial thrombocytosis caused by the Ser505Asn mutation *of the MPL gene* [4-8]. Although patients with *MPL*W515K also have a high allele load compared to *MPL*W515L, there were no significant differences in clinical and laboratory characteristics in these groups [12].

In most cases, the difficulties of studying the effect of mutations in *the MPL gene* on the course of ET are related to their rarity. Patients with three mutations (TN-status) remain the least studied category. The prognosis in patients with TN is currently recognized as unfavorable.

The discovery *of CALR mutations* plays an important role in the molecular diagnosis of MPN. *JAK2*V617F*, CALR*, and, more rarely, *MPL* are the main clonal markers of MPN [43]. It should be noted that *CALR mutations* were detected in 2 cases *of JAK2*-negative true polycythemia (IP) [15]. In addition, assessment of the mutational status *of JAK2, MPL*, and *CALR* is important not only for diagnosis, but also for prognosis of both thrombotic complications and overall survival [44].

Somatic mutations in the CALR gene were detected in 30-45% of MPN patients with the absence *of JAK2* and *MPL CALR* mutations. Patients with *CALR mutations* have a different disease phenotype from *those with JAK2*, *MPL*, or triple-negative mutations. ET occurs with a lower level of hemoglobin and the number of white blood cells, higher thrombocytosis and a low risk of thrombosis, and a high risk of post-platelet-induced MF. Patients are usually young, mostly male [22]. Family cases of ET with *the CALR mutation* are characterized by high thrombocytosis and a low rate of disease progression compared to cases with *the JAK2 mutation* [36].

Conflicting data have been obtained on the effect *of the CALR mutation* on the survival of ET patients. Better overall survival is reported in the group of patients with *the CALR mutation* compared to patients with Alzheimer's disease.

with *the JAK2 mutation* [22]. In the study conducted by J. Nangalia, no statistically significant differences were found [26].

In PMF patients*, CALR mutations* were associated with high thrombocytosis, normal white blood cell count, low anemia rate, and transfusion dependence on red blood cell suspension transfusion. The disease was mainly diagnosed at a young age, and patients were classified as low-risk according to the DIPSSplus scale [45].

ET in the presence of mutations in *the JAK2* and/or *CALR genes* — biologically, clinically and prognostically different forms of the disease. In ET, the presence *of the JAK2*V617F mutation increases the risk of thrombosis. Despite the fact that the carriage of mutations in *the CALR gene* is associated with significantly more pronounced thrombocytosis (platelets > 1000 $\times^{109}$/L) [26], the risk and frequency of thrombosis in this category of patients is lower than in ET patients with *the JAK2*V617F mutation. Patients with ET who carry mutations in *the CALR gene* are characterized by a decrease in the risk and frequency of thrombosis, and the course of the disease can be characterized as indolent [53, 9].

Thus, molecular genetic analysis *of JAK2*V617F, *JAK2* exon12, *MPL*W515K/L, and *CALR mutations* plays an exceptional role in the diagnosis of classic Ph-negative MPN. However, genes that control signal transmission within the cell, chromatin remodeling, DNA methylation, oncogenes, and tumor suppressors are involved in the occurrence and development of these diseases [27].

In addition to three somatic mutations (*JAK2*V617F*, MPL*, and *CALR*) that activate the JAK-STAT pathway, ET revealed a spectrum of different epigenetic rearrangements: *TET2, EZH2*,

ASXL1, CBL, IDH, IKZF1, LNK, and IDH1/IDH2. Somatic mutations *of the TET2, EZH2*, *DNMT3A*, *DNMT3A* and *ASXL1 genes* play a significant role in the pathogenesis of MPN and determine the phenotype and prognosis of the disease. Somatic mutations can occur prior to the appearance of a clone with *the JAK2 mutation*, simultaneously, or as a late molecular event during disease progression [21].

The lack of convincing data in favor of the specificity of such mutations for ET, their detection in other diseases of the blood system, organs of lymphoid and hematopoietic tissues: myelodysplastic syndrome (MDS), acute leukemia (OL), lymphoproliferative diseases (lymphomas), does not allow us to talk about the pathogenetic role of these rearrangements and their inclusion in the diagnostic algorithm of ET in as highly specific molecular genetic markers of clonality. However, the contribution of epigenetic mutations to the emergence and development of ET requires further study.

The TP53 gene encodes a tumor suppressor protein involved in regulating the expression of target genes that regulate the cell cycle, apoptosis, and DNA repair. Loss of gene function is associated with the appearance of various human malignancies. Mutation of the TP53 gene was detected in 45.5% of MPN in the blast crisis phase and only in 4% in the chronicophase [34]. Thus, TP53 mutations play an important role in the process of disease transformation.
Thus, molecular genetic analysis *of JAK2*V617F, *JAK2* exon12, *MPL*W515K/L, *CALR* , and TP53 mutations plays an exceptional role in the diagnosis of classic Ph-negative MPN. However, genes that control signal transmission within the cell, chromatin remodeling, DNA methylation, oncogenes, and tumor suppressors are involved in the development of these diseases. Current knowledge suggests that *the JAK2*V617F mutation cannot be the first event in the complex pathogenesis of MPN [15].

However, despite modern advances in understanding the etiology and pathogenesis of the disease, there is currently no empirically confirmed, unified and generally accepted concept of the pathogenesis of ET. The leading hypothesis of the pathogenesis of the disease is polyethological. Predisposition to the development of ET, as well as other diseases of the Ph'-negative MPN group, is realized when the hematopoietic stem cell is exposed to various external factors that damageë its genome with subsequent malignant transformation of the cell [41, 42]. Under the predisposition, the carrier of various genetic changes is considered. Thus, carriage of haplotype 46/1 *of the JAK2 gene* is associated with a significant increase in the risk of V617F rearrangement in *the JAK2 gene* [11, 41].

Additional studies are needed to clarify the role of other molecular events in the formation of the phenotype of each individual nosology in the Ph-negative MPN group. The new data are of indisputable importance for the synthesis of targeted drugs.

External agents, the action of which causes the appearance of clonal rearrangement of a normal cell, are factors of a physical and chemical nature, various viral and bacterial agents. At the same time, the action of external damaging factors can provoke the development of chronic inflammation. The inflammatory process, in turn, is a stimulator of hematopoiesis and, including, myelopoiesis. In addition, a prolonged inflammatory process increases the risk of cell DNA damage, which may also be one of the reasons for the appearance of genetic defects in hematopoietic cells [21]. At the same time, chronic inflammation is manifested by increased production of pro-inflammatory cytokines. Prolonged increases in cytokine concentrations also

contribute to damage to the cellular genome. Thus, a chronic autoimmune or inflammatory process accompanied by an increased concentration of cytokines in the blood is a factor contributing to the development of ET in predisposed individuals [50].

The influence of external factors combined with the presence of a genetic predisposition is realized in the appearance of a genetic disorder – a mutation at the level of a polypotent hematopoietic progenitor stem cell. As a result of the genetic rearrangement that triggers the myeloproliferative clonal process, a clone of myeloid hematopoiesis progenitor cells is formed.

Unfortunately, at present we can only talk about probable genetic events responsible for the development of malignant transformation of a normal hematopoietic stem cell. There are no convincing experimental data that allow unambiguously accepting any of the known gene mutations as a pathogenetic event that initiates the clonal process [2, 1, 33, 17].

At the present stage, the question of the possible influence of somatic mutations *of the JAK2, MPL*, and *CALR genes* on the clinical course and prognosis of ET remains open. The data published in various literature sources do not allow us to make a complete and systematic description of the development, clinical course, and prognosis of ET in carriers of various genetic rearrangements. In addition, possible combinations of somatic mutations with epigenetic rearrangements and chromosomal aberrations, their impact on the course, risks of complications, and modification of the prognosis of the disease need to be studied.

In recent years, significant progress has been made in deciphering the molecular and genetic mechanisms of ET, which has made it possible to create a new class of drugs with pathogenetic effects.
The goal of modern ET therapy is to prevent vascular catastrophes, control the progression of the disease and stop its symptoms, while improving the quality of life of patients [40].
Adequate diagnosis and regular monitoring of treatment using clinical, morphological, cytogenetic and molecular genetic research methods is a prerequisite for correct prediction of the course of the disease and achieving maximum effectiveness of therapy. Currently, there are no generally accepted standards for the diagnosis and treatment of ET in Russian clinical practice.
Therefore, thestudy of ET should be continued in order to identify and describe new specific molecular genetic markers of clonality, which may contribute to a deeper understanding of the nature of this malignant myeloproliferative disease.

It seems appropriate to study the impact of genetic rearrangements on the clinical course, possible potentiation of the risks of complications, and the overall prognosis of ET.

The data available in the literature on the role of these individual genetic markers are few and contradictory. Only a detailed study of the population features of the above-mentioned genetic mutations and an assessment of the correlation between the genotype and phenotype of the disease can make it possible to choose the right strategy for early diagnosis and prognosis, as well as the development of preventive measures for thromboembolic and hemorrhagic complications in patients with ET. Unfortunately, there are still quite rare publications in which the authors analyze the so-called risk factors for the development of the above-mentioned complications in ET. Finally, there are many unresolved questions regarding the feasibility of diagnosing certain gene polymorphisms in clinical practice, which is largely due to the insufficient number of studies aimed at establishing correlative relationships between the features of the clinical course of ET

and the presence of certain markers in the patient's genotype. The question of which interactions of acquired and genetic factors, as well as gene-gene combinations, determine the predisposition to the development of thrombosis and hemorrhage, and the features of the course remains open. The need to use fundamentally new approaches in studying the basis of genetic predisposition to such types of complications in ET is dictated by the current concept of the polygenic nature of myeloproliferative diseases, which postulates the presence in the vast majority of cases of thromboembolic diseases of not one, but several genetic variants that independently or synergistically modify the risk of developing the disease.

The obtained data will improve the assessment of the clinical and prognostic significance of the carriage of molecular genetic rearrangements in ET and will contribute to updating therapeutic approaches and algorithms, which will optimize the treatment and personalize the tactics of therapy for this disease.

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